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Fatigue in Inflammatory Bowel Disease (IBD): Diagnostic Workup and Management

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Fatigue in Inflammatory Bowel Disease (IBD): Diagnostic Workup and Management

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Introduction

Fatigue affects up to 72% of patients with inflammatory bowel disease (IBD), including up to 1 in 2 patients whose disease is in remission.¹

Beyond IBD treatments, few therapies for fatigue have been studied. The lack of clear success in clinical trials investigating fatigue treatments in IBD has left many clinicians without the therapeutic arsenal to manage this symptom.

This paper aims to provide a practical roadmap for busy clinicians to understand and incorporate IBD-related fatigue discussions within their consultations.

Recognizing and Assessing Fatigue

The burden of disease for patients often exceeds digestive manifestations, such as diarrhea, rectal bleeding, and pain.² Beyond these, fatigue is one of the most frequently non-gastrointestinal patient-reported complaints, yet remains under-recognized and under-discussed by clinicians.^{2,3} Understanding how to recognize and measure fatigue is an important first step in its management.

Fatigue is more than generic tiredness that can affect both physical and mental functioning. Some level of fatigue is common, but it should not be exhaustive or limiting. The aim of assessment is to recognize that some level of fatigue is expected

Feature	IBD Fatigue Scale (IBD-F)	FACIT-Fatigue
Structure	2 sections: 5 items on frequency/severity of fatigue 30 items on experience/impact of fatigue	13 items total
Item content	Section I: measures both how often fatigue occurs and its severity Section II: measures the impact of fatigue across physical, cognitive, emotional, and functional daily activities	Physical tiredness/weakness items, plus functional-impact items (e.g. energy levels, ability to perform usual activities, need to rest or sleep)
Recall period	2 weeks	1 week
Response scale	0–4 Likert scale	0–4 Likert scale
Direction of score	Higher score = greater fatigue	Higher score = less fatigue
How the total is calculated	Sections scored separately; not combined into one total score Section II has six items with an N/A option; the total is prorated when N/A responses are selected	Sum individual item scores, multiply by 13, divide by the number of items answered Note: Negatively worded items are recoded, so 0 = bad, 4 = good
Score range	Section I: 0–20 Section II: 0–120	0–52 total
Clinically useful cut off	Varies between studies	None (>40), mild (>30 to ≤40), moderate (>21 to ≤30), and severe (≤21) ⁶

Figure 1. IBD-F vs FACIT-Fatigue assessment tools; courtesy of Yaa Danso, MBBS, MRCP, IBD Research Fellow, Prof. Ailsa L. Hart, James Alexander, MD, and Calum D. Moulton, MD.

but fatigue should not be severe enough to impair daily functioning.

A fatigue assessment tool can establish symptom severity and guide further conversations. Two commonly used tools are highlighted above (**Figure 1**). One of these, the IBD Fatigue (IBD-F)⁴ scale, is split into the two sections; the first section incorporates five brief questions that establish fatigue severity over the last 2 weeks. This scale is validated within IBD and can be easily completed by patients before their consultation. Scores range between 0 and 20, with scores of 11 or more suggesting severe fatigue. This tool can be used regularly to track changes in fatigue severity over time. However, within the IBD-F, there is no formal cut off to delineate improvement in fatigue over time.⁴ Subsequent studies have examined this issue and have proposed differing Score1 cut-offs, while others have not identified any threshold.¹ The Functional Assessment of Chronic Illness Therapy—Fatigue scale (FACIT-F)⁵ is an alternative assessment tool. This 13-item questionnaire evaluates fatigue symptoms experienced over the previous week. Because this tool is used across a range of conditions, FACIT-F

scores can be compared with other chronic diseases. However, its more complex scoring may limit its practicality within time pressured clinics.

A practical tip is to build fatigue assessment into routine care for all patients. Doing so ensures that patients understand that fatigue is recognized as an important symptom in its own right and will also help to build our knowledge base of how patients experience fatigue.

Understanding the Mechanisms

Fatigue is well recognized among patients with active disease; however, far more complex is the persistence of fatigue in quiescent IBD.

Fatigue is observed in chronic inflammatory diseases, such as multiple sclerosis and systemic lupus erythematosus, which supports the hypothesis that inflammatory cytokines could contribute to fatigue.⁷ Elevated levels of proinflammatory cytokines have been shown in fatigued patients, further supporting an inflammatory cytokine-mediated mechanism.^{8,9} The brain-gut axis is the bidirectional pathway between the central and enteric nervous systems.

In response to environmental or clinical stressors, proinflammatory cytokines can activate the hypothalamic-pituitary-adrenal axis, leading to cortisol dysregulation in which cortisol is released. These neuroendocrine changes may have systemic effects and can affect the brain, resulting in fatigue.¹⁰ Within healthy individuals, sleep deprivation, which itself exacerbates fatigue, is associated with an increase in circulating proinflammatory cytokines.¹¹

Mood disorders, which can also cause fatigue,¹² are mediated through central neurotransmitters, primarily serotonin (5-hydroxytryptamine), dopamine, and noradrenaline. The synthesis of these neurotransmitters requires the availability of tryptophan and tyrosine.¹³ As branched-chain amino acids (BCAAs) compete with tryptophan and tyrosine for the same transporters to pass the blood-brain barrier, alterations in circulating BCAA levels are hypothesized to influence the availability of these neurotransmitters in the brain, leading to fatigue. Experimental mouse models of colitis have shown new-onset depressive and anxiety-like symptoms after the induction of gut inflammation.^{13,14}

The Diagnostic Workup

The mechanisms underlying fatigue within IBD are not fully understood; however, identifying and addressing potentially reversible causes is a key component of management. A common challenge faced by clinicians is how to proceed when a patient reports fatigue.¹⁵ The following section outlines a practical approach to assessment and management.

Minimizing mucosal disease activity is an important component of fatigue management. Assessing disease activity with endoscopy or imaging can be helpful. However, we suggest doing this only when supported by gastrointestinal symptoms or biochemical markers as fatigue often remains severe in the context of quiescent disease.

In addition to evaluating disease activity, nutritional and hematological investigations can prove useful. Iron deficiency, reflected by low ferritin levels, irrespective of anemia, can be a driver of fatigue. Assessment of vitamin B12 and folate status are relevant for patients with ileal Crohn's disease or post ileal resection.

Extraintestinal manifestations of IBD, primary sclerosing cholangitis, and coexisting

autoimmune disorders such as hypothyroidism are common within the IBD population and should be addressed. A review of medications is also important. Corticosteroids disrupt sleep patterns, and over time may contribute to myopathy and fatigue, while thiopurines are also recognized to cause fatigue in some patients. Although an exhaustive medication review is not necessary in every case, clinicians should be aware of commonly used medications that can impact fatigue.

Psychological comorbidities can coexist with IBD-related fatigue or contribute to fatigue independently. Conditions such as depression and anxiety are potential causes of fatigue and are treatable. Screening tools such as the Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) can help identify symptoms of depression and anxiety, respectively. When these conditions are identified, appropriate management should be initiated, either within the multidisciplinary IBD team or by involving primary care.

Non-pharmacological Management

Non-pharmacological therapies require adherence. It is important to recognize that even with an active and willing patient non-pharmacological therapies are not always successful.

Patient-led sleep hygiene techniques can be used successfully prior to and alongside pharmacological therapies. Four key techniques include: **1)** avoiding alcohol and caffeine 4 hours before bedtime; **2)** avoiding 'screen time' in bed and at least one hour prior; **3)** obtaining daytime sunlight exposure to help maintain circadian rhythms; and **4)** maintain a consistent sleeping time and waking time, even if sleep has been poor.^{16,17} Better sleep quality may be achieved through daytime behavioural activation. Measures such as exposure to sunlight and limiting daytime napping help to distinguish between daytime activities and nighttime rest can help regulate circadian rhythms.

IBD-related fatigue can vary in severity over time for the same patient. On days when fatigue is less pronounced, patients may take advantage of this extra capacity to catch up on lost productivity and consequently overexert themselves. While understandable, this all-or-nothing approach is often followed by worsening in fatigue over the following days, precipitating a 'boom-and-bust'

pattern of fatigue.¹ Opting for sustainable regular activity is often more beneficial, although this requires confirmation within a randomized controlled trial (RCT).^{18,19}

Pharmacological Therapies

If sleep is a concern and non-pharmacological therapies have been unsuccessful, the use of nocturnal sedative medications can be considered.

However, we discourage the use of benzodiazepines and Z-drugs (e.g., zolpidem, eszopiclone, and zopiclone), owing to their risk of dependence and their potential to impair state-dependent learning. The latter refers to the phenomenon whereby information learned in a particular internal state is most easily recalled when that same state is reproduced. Consequently, psychological work that is completed while treated with Z-drugs, may not be as readily retained or transferred to periods when the medication is no longer being used.¹

Non-addictive Sedating Medications

Amitriptyline may be particularly useful for patients with comorbid pain symptoms.²⁰ Treatment is initiated at 10 mg taken once nightly (ON), and can be increased to 30 mg as needed.²¹

Mirtazapine, a sedative antidepressant, may be helpful for patients in whom depression or anxiety is prominent, or for those with persistent upper gastrointestinal symptoms such as postprandial fullness or nausea.²² Patients should be advised that daytime sedation can be pronounced during the first week of treatment but often diminishes with continued use.²³ The usual starting dose of mirtazapine is 15 mg ON.²⁴ Notably, the 15 mg dose is generally as sedating as higher doses.²²

Daridorexant, a dual orexin receptor antagonist for the treatment of insomnia, was shown to be generally safe and well tolerated in a 52-week study (not specifically in IBD) and was associated with minimal morning drowsiness.²⁵ The usual starting dose is 50 mg taken ON, though lower doses of 25 mg may be more appropriate for those with liver impairment.

Emerging evidence suggests that melatonin may function as a mediator between gut microbiota disorders and sleep deprivation.²⁶ In the UK, melatonin is licensed for adults over 55 years of age, with a usual starting dose of 2 mg ON, and a maximum dose of 10 mg ON.²⁷

Patients should be advised that sedative medications may cause residual drowsiness the next day, especially during the early stages of treatment. Caution should be explicitly provided regarding activities that require alertness, including driving, operating heavy machinery, or performing skilled tasks. Use of alcohol should be minimized to prevent oversedation.

Alerting medications can also be considered for patients with refractory fatigue, although their use in this context is off-licence. Modafinil is a wakefulness-promoting medication that acts as an atypical dopamine reuptake inhibitor by binding to the dopamine transporter, which increases extracellular dopamine levels in the brain, although its exact mechanism of action is not clearly defined. In the UK, modafinil is licensed for treating narcolepsy, though its use beyond this indication is supported by the Maudsley Guidelines.²³

Modafinil is initiated at 100 mg in the morning, although a lower starting dose of 50 mg may be appropriate for patients who may be more susceptible to side effects (**Figure 2**). The clinical benefits of modafinil are usually rapid, frequently within 1 week. The efficacy of modafinil should be assessed ideally within 8 weeks and should only be continued if it is beneficial and well tolerated.

Modafinil should be avoided in patients with known arrhythmias, cor pulmonale, left ventricular hypertrophy, and moderate-to-severe uncontrolled hypertension.²⁸ Modafinil is contraindicated during pregnancy, owing to associations with birth defects, and it may reduce the effectiveness of some hormonal contraceptives.²⁹ Women of childbearing age starting modafinil should be advised to use appropriate contraception, such as intrauterine devices, barrier methods, depot progestogen preparations, during treatment and for 2 months after discontinuation.

Although the therapies described above have shown potential for managing IBD-related fatigue, evidence from RCTs is currently lacking (**Figure 2**).

Reassessment and Follow-up

If a pharmacological treatment is effective, we recommend ongoing review at 6 month intervals. At present, there is insufficient evidence to guide the duration of pharmacotherapy for IBD-related fatigue, whether using sedative or wakefulness-promoting medications. We follow extrapolated guidance from depression management with antidepressants, which is to continue any effective medication for 6–9 months,

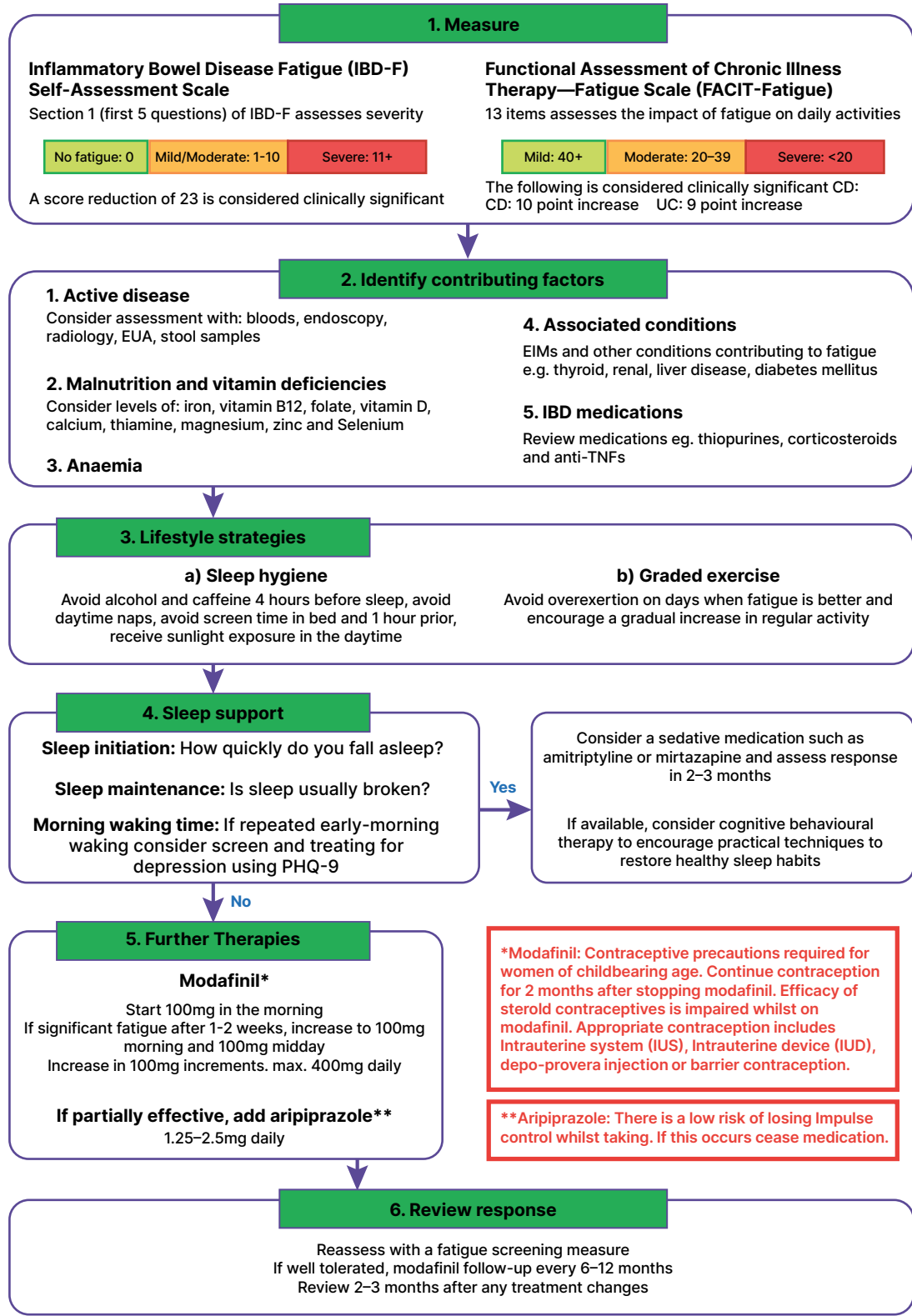


Figure 2. Treatment algorithm for IBD fatigue; courtesy of Yaa Danso, MBBS, MRCP, IBD Research Fellow, Prof. Ailsa L. Hart, James Alexander, MD, and Calum D. Moulton, MD.

Abbreviations: CD: Crohn's disease; EIMs: extraintestinal manifestations; EUA: examination under anaesthesia; PHQ-9: Patient Health Questionnaire-9; UC: ulcerative colitis

before considering dose reduction and/or discontinuation.²⁶ During the initial treatment phase, we suggest reassessing the response at 8 weeks, using the same fatigue assessment tool employed at baseline.

Successful assessment of IBD-related fatigue is not a singular event; rather, it is an ongoing process that requires regular review and dialogue with the patient. Effective management includes a combination of strategies, such as patient-led immediate measures, pharmacological therapies, and the identification and exclusion of other potential contributors to fatigue. Similarly, successful treatment is not a single intervention; we therefore suggest acknowledging and describing this premise at the beginning of treatment, and throughout the treatment course.

Unmet Needs

Despite its high prevalence and significant impact on quality of life, fatigue often remains under-recognized and under-discussed during consultations, perhaps as a consequence of uncertainty regarding management options. The importance of this unmet need is highlighted by the inclusion of fatigue among the James Lind Alliance's top 10 research priorities.³⁰ Fostering active questioning about fatigue during clinical encounters is an important first step.

Despite investigation, a specific cause of fatigue often cannot be identified. This knowledge gap makes IBD-related fatigue an important area of interest for future research, with the potential to improve our understanding of its underlying mechanisms and to support the development of novel targeted treatments. Currently evidence from RCTs is insufficient to support any single treatment approach. This highlights an opportunity to prioritize IBD-related fatigue as a research focus, particularly in relation to alerting medications. If successful, these treatments can have a palpable and direct improvement in patients' quality of life.

Conclusion

Regular use of validated assessment tools for fatigue will provide insight into our understanding of how the landscape of fatigue evolves over time and help evaluate the effectiveness of emerging therapies.

In clinical practice, proactive identification of fatigue, targeted investigations for reversible causes, and ongoing reassessments form the basis for practical steps to managing IBD-related fatigue.

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Management of Steroid-Refractory
Immune Checkpoint Inhibitor
Colitis: A Practical Guide to
Advanced Therapies

Rami Habib, MD

Wilson H. Miller Jr., MD, PhD

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Key Takeaways

When to escalate: Patients with steroid-refractory or steroid-dependent immune checkpoint inhibitor colitis should receive advanced immunosuppressive therapy. Earlier escalation should be considered when endoscopy demonstrates high-risk features, particularly deep ulcerations, which predict steroid failure.

Which agent to choose: Infliximab and vedolizumab are the preferred advanced therapies and have comparable efficacy. Agent selection should be individualized based on the clinical context: infliximab is generally preferred for acute, severe disease requiring rapid control, whereas the gut-selective mechanism of vedolizumab may be favoured when immune checkpoint inhibitor rechallenge is anticipated.

How long to treat: At least three induction doses are recommended; however, treatment duration should be guided by objective markers of disease activity, such as fecal calprotectin levels and endoscopic mucosal healing, rather than by the number of doses alone. The intent to resume checkpoint-inhibitor therapy does not dictate the number of induction infusions but may support adding maintenance biologic therapy at the time of rechallenge to reduce recurrence risk.

Introduction

The advent of immune checkpoint inhibitors (ICI) has revolutionized cancer therapy by leveraging the immune system's ability to recognize and eliminate malignant cells.¹ These agents are engineered monoclonal antibodies that disrupt inhibitory immune checkpoints that normally restrain T-cell activity, thereby enhancing antitumour immune responses.² Despite their transformative impact, ICI can precipitate off-tumour immune-related adverse events (irAEs), which may involve any organ system. Among these, colitis, with or without enteritis, is one of the most common and clinically significant gastrointestinal (GI) side effects caused by ICI therapy, particularly in patients receiving cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) agents.³

In patients who present with colitis or acute diarrhea, the initial step is to exclude alternative causes, particularly infectious causes

(e.g., *Clostridioides difficile*, invasive bacterial enterocolitis, and, in certain circumstances, cytomegalovirus colitis). Once the clinical picture and investigations support ICI colitis as the most probable diagnosis, severity should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (see **Table 1**). This system grades severity using stool frequency and features such as hematochezia and mucus, together with clinical parameters including the need for hospitalization or intensive care and hemodynamic instability.⁴ These criteria can both underestimate and overestimate the true severity of ICI colitis, as discussed below.⁵

Management of irAEs typically involves corticosteroids due to their broad immunosuppressive effects.⁶ However, corticosteroids come with their own set of well-recognized side effects including immunosuppression, hyperglycemia, and bone loss. Initial corticosteroid therapy varies by colitis severity: grade 1 disease is managed

Grade	Diarrhea	Colitis/Enterocolitis
1	Increase of <4 stools/day over baseline; mild increase in ostomy output	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Increase of 4–6 stools/day over baseline; moderate increase in ostomy output; limiting instrumental ADL	Abdominal pain; mucus or blood in stool
3	Increase of ≥7 stools/day over baseline; hospitalization indicated; severe increase in ostomy output; limiting self-care ADL	Severe or persistent abdominal pain; fever; ileus; peritoneal signs
4	Life-threatening consequences; urgent intervention indicated	Life-threatening consequences; urgent intervention indicated
5	Death	Death

Table 1. CTCAE v5.0 severity grading for diarrhea, colitis, and enterocolitis; *adapted from National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE) v5.0, 2017 (public domain).*

Definitions: **Diarrhea:** increased frequency and/or loose or watery stools; colitis, inflammation of the colon; **Enterocolitis:** inflammation of the small and large intestine. A semicolon denotes “or” within a grade. **ADL:** activities of daily living. Grades are based predominantly on clinical symptoms and do not incorporate endoscopic findings.

supportively without steroids, whereas grade 2 receives prednisone or IV methylprednisolone 1–2 mg/kg/day and grade 3–4 receives IV methylprednisolone 1–2 mg/kg/day. Furthermore, up to 20% of patients requiring steroids for an irAE are steroid refractory, necessitating escalation to alternative immunosuppressive agents.⁷ Current management guidelines for such refractory cases rely largely on expert consensus and draw parallels from treatment paradigms in primary autoimmune diseases, notably inflammatory bowel disease for the management of ICI colitis.⁸ When dealing with ICI colitis, three key questions must be answered. What is the right time to start advanced therapy? Which agent is best to use? How long should advanced immunosuppression be maintained?

When to Start Advanced Therapy

Two clinical scenarios should prompt escalation beyond corticosteroids: steroid-refractory disease and steroid-dependent disease. Steroid-refractory ICI colitis is defined as the absence of meaningful clinical improvement after approximately 72 hours of adequate-dose intravenous corticosteroids (methylprednisolone 1–2 mg/kg/day).^{5,9} Steroid-dependent disease refers to the recurrence of colitis symptoms during or shortly after completing the glucocorticoid taper, which leads to re-escalation and consideration of steroid-sparing therapy.⁵ Both

the American Gastroenterological Association (AGA) Clinical Practice Update and the American Society of Clinical Oncology Guideline Update converge on these definitions, while the National Comprehensive Cancer Network (NCCN) guidelines similarly recommend additional immunosuppression if there is no response within 1–2 days for grade 3–4 colitis or within 3 days for grade 2 colitis.^{9,10} Importantly, the approximately 72-hour threshold is based on expert consensus, retrospective observation and extrapolated from the management of severe ulcerative colitis presentations rather than prospective trials designed to validate a specific time point. The consensus of the guidelines on this threshold reflects clinical pragmatism between allowing sufficient time to observe a steroid response while being short enough to avoid complications of uncontrolled inflammation.

The decision to escalate therapy should not be based solely on time. Baseline clinical and endoscopic features can identify patients at high risk of steroid failure before the 72-hour threshold arrives. Among these, colonic ulceration on initial endoscopy is the strongest and most consistently validated predictor of steroid-refractory disease. The AGA update identifies endoscopic ulceration as the only established factor associated with the need for secondary immunosuppression, and notably, CTCAE symptom grading is not predictive.⁵ The NCCN guidelines reinforce this finding, noting that endoscopic ulceration is associated with a greater likelihood of

Feature	Infliximab	Vedolizumab
Class/mechanism	Chimeric monoclonal anti-TNF-α antibody; broad suppression of TNF-mediated inflammation across tissues	Humanized anti-α4β7 integrin antibody; blocks lymphocyte trafficking to the gastrointestinal mucosa
Typical dose	5 mg/kg IV	300 mg IV
Induction schedule	Weeks 0, 2, and 6 (IBD-adapted)	Weeks 0, 2, and 6 (IBD-adapted)
Onset of action	Rapid, often within days	Slightly slower, but comparable in prospective data (median time to improvement approximately 3 days)
Clinical remission	High (approximately 90% in the randomized comparison)	High (approximately 89% in the randomized comparison)
Key cautions/relative contraindications	Hematologic malignancy (rare lymphoma risk), severe congestive heart failure, concurrent ICI hepatitis (drug-induced liver injury) Screen for tuberculosis and hepatitis B; exclude bowel perforation	Theoretical interference with mucosal antitumor responses in primary GI malignancies or GI metastases; fewer systemic infectious concerns
Effect on antitumor immunity	Systemic mechanism; preclinical models suggest TNF blockade may not impair ICI efficacy	Gut-selective mechanism theoretically spares systemic antitumor immunity, though it may affect mucosal responses in GI tumours
Best-suited scenario	Acute, severe, or fulminant colitis requiring rapid control; concurrent extra-intestinal irAEs needing systemic immunosuppression	When gut-selective control is preferred: planned ICI rechallenge, higher infection risk, or concern for recurrence

Table 2. Comparison of infliximab and vedolizumab for advanced (steroid-sparing) therapy in immune checkpoint inhibitor colitis; *courtesy of Rami Habib, MD, Wilson H. Miller Jr., MD, PhD, and Khashayar Esfahani, MD.*

Abbreviations: **GI:** gastrointestinal; **IBD:** inflammatory bowel disease; **ICI:** immune checkpoint inhibitor; **irAE:** immune-related adverse event; **IV:** intravenous; **TNF:** tumour necrosis factor.

corticosteroid failure and that initiating biologic therapy early in these patients may reduce the risk of disease recurrence.¹⁰ In addition to endoscopic assessment, stool biomarkers can be used as a non-invasive stratification layer. The NCCN recommends measuring fecal calprotectin and lactoferrin at initial assessment across all colitis grades, with serial calprotectin monitoring every 2 months to guide treatment duration.¹⁰ Taken together, these data support a risk-stratified approach. In patients with deep or extensive ulceration, markedly elevated calprotectin, or other high-risk features, there is a rationale for pre-emptive escalation to selective immunosuppressive therapy (SIT) rather than waiting for formal steroid failure. This approach represents the strongest opportunity to improve outcomes, because the current “fail-then-escalate” approach exposes the highest-risk patients to the longest steroid courses and a greater risk of complications.

The strategy of upfront biologic therapy, defined as initiating infliximab or vedolizumab concurrently with or shortly after corticosteroid treatment rather than sequentially, has gained support in observational studies. A large propensity-matched real-world analysis comparing early biologic initiation (within 3 days of colitis diagnosis) to delayed initiation (days 3–14) found numerically favourable outcomes with early therapy across mortality, hospitalization, and long-term corticosteroid use, although these differences did not reach statistical significance.¹¹ A single-centre retrospective study of prophylactic vedolizumab in high-risk patients, including those with prior severe ICI colitis or pre-existing inflammatory bowel disease (IBD), demonstrated markedly reduced diarrhea severity and eliminated the need for corticosteroid treatment.¹² Prospective trials, including NCT04407247, are needed to confirm whether these findings represent a true therapeutic benefit or reflect unmeasured confounding.¹³ Until those

data mature, the following points remain relevant: guidelines endorse early escalation in patients with endoscopically severe disease, observational data suggest benefit from upfront biologic therapy, and the existing evidence base remains insufficient to justify a universal change in practice.

Choice of Advanced Therapy

Infliximab and vedolizumab represent mechanistically distinct approaches to steroid-refractory ICI colitis (see Table 2 for a detailed comparison). Infliximab broadly suppresses tumour necrosis factor (TNF)-mediated inflammation, whereas vedolizumab selectively blocks lymphocyte trafficking to the GI tract.^{5,14} Both agents are typically administered on an IBD-adapted induction schedule at weeks 0, 2, and 6; however, responses in ICI colitis occur far more rapidly than in IBD, generally within one week.⁵ Preliminary results from the first randomized controlled trial comparing the two agents (NCT04407247) have been reported in abstract form. Among 19 of 22 evaluable patients, clinical remission rates at 2 weeks were similarly high (infliximab 90% vs. vedolizumab 88.9%), with a median time to symptom improvement of 3 days in both treatment arms. Steroid-free remission at one month was achieved in 80% and 77.8% of patients, respectively, and recurrence rates did not differ significantly (40% vs. 33.3%).¹³ These findings are consistent with a meta-analysis of eight retrospective studies, which demonstrated no significant difference in remission rates between the two monotherapies. Although vedolizumab was associated with a higher rate of colitis recurrence (odds ratio [OR] 0.32, 95% confidence interval [CI] 0.19–0.53) it was also associated with a significantly lower overall corticosteroid usage (mean difference –18.29 days).¹⁵ Similarly, the largest single-centre retrospective study (n = 1,151 patients with ICI colitis) reported comparable efficacy with infliximab producing a shorter time to clinical response.¹⁶ (See Table 2.) In clinical practice, agent selection is driven by clinical context rather than by clear efficacy differences. Infliximab is used in severe and urgent cases given its faster onset of action and greater clinical experience in this setting.¹⁷ However, infliximab should be avoided in patients with hematologic malignancies (given the role of TNF-α in antitumor immune surveillance), in

those with severe congestive heart failure (given demonstrated cardiac harm even with short-course use), in patients with concurrent ICI hepatitis (given the risk of drug-induced liver injury) and weighed carefully in patients with significant comorbidities or elevated infection risk. While these complications vary in frequency, vedolizumab is recommended as a gut-selective alternative that avoids these risks.⁵ The gut-selectivity of vedolizumab is its main theoretical advantage. By confining immunosuppression to the GI tract, vedolizumab may preserve systemic antitumor immunity and is therefore particularly attractive for patients in whom ongoing or future ICI therapy is planned.¹⁴ However, because vedolizumab acts locally in the gut, the AGA update cautions that it could attenuate mucosal antitumor immunity in patients with tumours in the GI tract, namely primary GI cancers or GI metastases, and flags this as a relevant consideration in treatment selection.⁵ For patients with concurrent extra-intestinal irAEs requiring systemic immunosuppression, infliximab’s broader mechanism may offer the advantage of treating multiple toxicities simultaneously. Infection risk should also be considered. Unlike inflammatory bowel disease, where steroids are used at lower doses but maintenance immunomodulator therapy and prolonged tapering are the norm, ICI colitis is treated with higher weight-based steroid doses as detailed above but a deliberately shorter taper, typically over 4–6 weeks after symptoms improve to grade ≤1, and maintenance immunosuppression is far less often required.¹⁸ When a biologic (infliximab or vedolizumab) has been added, guidelines recommend compressing the taper further, to under 2–4 weeks, specifically to limit cumulative steroid exposure and the resulting risk of infection.¹⁰ For patients refractory to both infliximab and vedolizumab, the evidence base narrows considerably. The NCCN suggests tofacitinib, a Janus kinase inhibitor, and ustekinumab, an anti-interleukin-12/23 antibody, as potential treatments for dual-refractory colitis.¹⁰ In addition, fecal microbiota transplantation has demonstrated approximately 75% efficacy in a small series of 15 refractory cases.¹⁹ Other therapies, including calcineurin inhibitors (tacrolimus) and extracorporeal photopheresis have been described in case-based evidence.^{5,17} Given that many of these options carries a risk of interfering

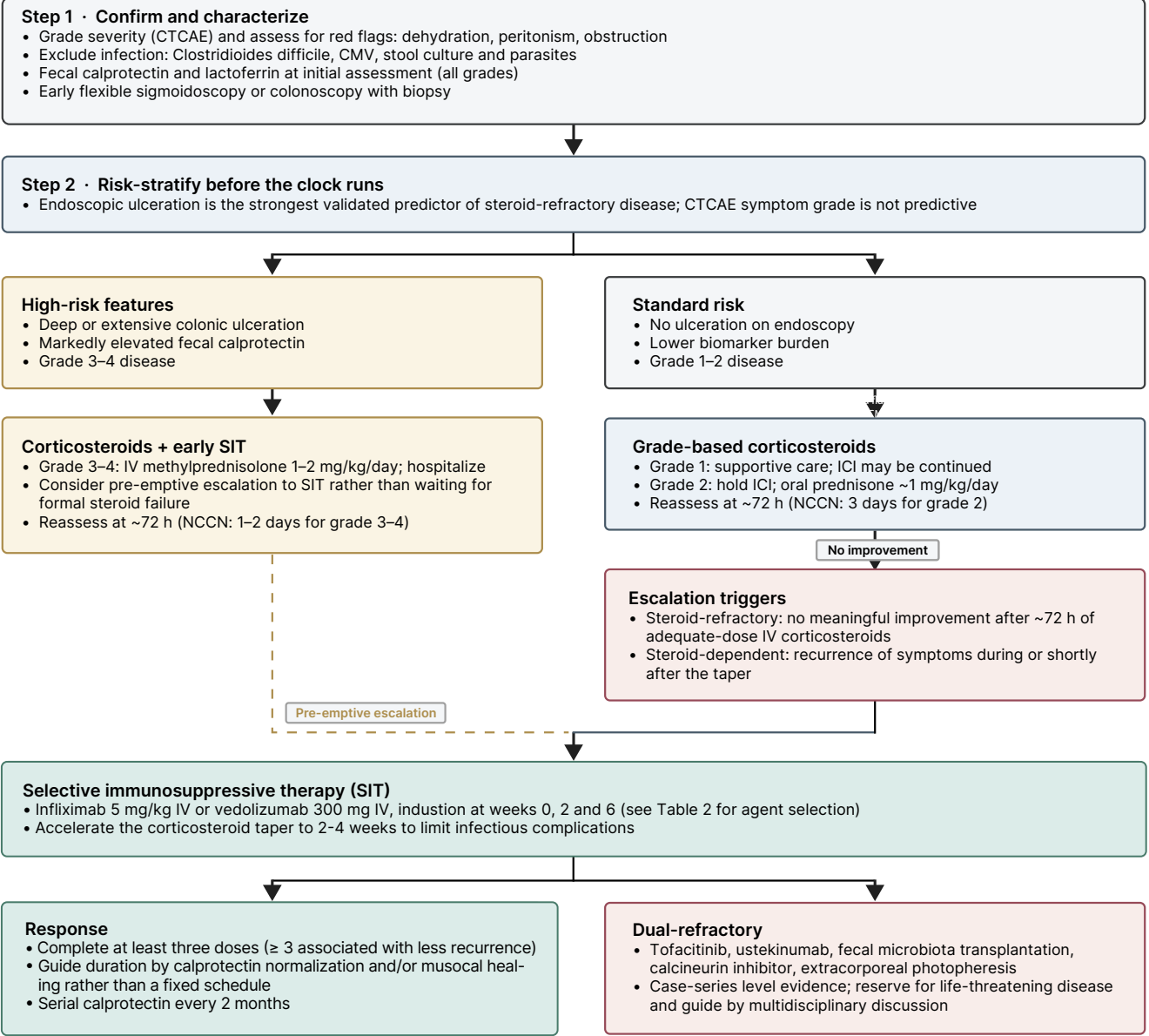


Figure 1. Risk-stratified escalation flow diagram in immune checkpoint inhibitor-induced colitis; courtesy of Rami Habib, MD, Wilson H. Miller Jr., MD, PhD, and Khashayar Esfahani, MD.

Abbreviations: ICI: immune checkpoint inhibitor; CTCAE: Common Terminology Criteria for Adverse Events; CMV: cytomegalovirus; IV: intravenous; SIT: selective immunosuppressive therapy; NCCN: National Comprehensive Cancer Network.

with antitumor immunity and that the evidence remains at the case-series level, their use should be reserved for life-threatening, multiply refractory disease and guided by multidisciplinary discussion.

Duration of Therapy

The optimal duration of biologic therapy for ICI colitis is not firmly established; however, retrospective data and guidelines support

a minimum of three infusions (at weeks 0, 2, and 6) as the standard induction course. The NCCN guidelines note that “receipt of three or more doses has been associated with less frequent colitis recurrence.”¹⁰ Corticosteroid tapering should proceed in parallel. When corticosteroids are used alone, guidelines recommend tapering over 4–6 weeks, whereas with coadministration of infliximab or vedolizumab, an accelerated taper over 2–4 weeks is recommended to reduce

the risk of infectious complications.¹⁰ Rather than adhering to a fixed treatment duration, objective endpoints should guide the decision to discontinue therapy. The NCCN endorses serial fecal calprotectin monitoring (every 2 months) and repeat endoscopy to assess mucosal healing as tools to guide treatment duration, although neither are mandatory.¹⁰ Neither guidelines nor prospective data define a fixed interval for repeat endoscopy; it is reserved for confirming mucosal healing when it will change management, i.e. before ICI rechallenge and for re-evaluating refractory, persistent, or recurrent disease (with ileocolonoscopy when a prior limited exam was unrevealing).¹⁴ In clinical practice, treatment is continued until symptoms improve to grade ≤ 1 and, ideally, until calprotectin normalizes or endoscopic remission is confirmed. Patients presenting with deep ulceration or recurrent flares may require maintenance therapy beyond the standard three-dose induction.

Whether to continue maintenance biologic therapy when restarting the checkpoint inhibitor is among the most clinically consequential and least evidence-supported decisions in the management of ICI. The NCCN Principles of Immunotherapy Rechallenge recommend considering concurrent vedolizumab on immunotherapy resumption for patients with prior grade 2–3 colitis.¹⁰ Supporting this approach, a multicenter retrospective study of 138 patients has shown that concurrent SIT (infliximab or vedolizumab) during ICI rechallenge was independently associated with a reduced risk of severe colitis recurrence (OR 0.34, 95% CI 0.13–0.92) without a negative impact on survival outcomes.²⁰ Across ICI classes, the overall risk of recurrent ICI colitis upon rechallenge is approximately 30–37%, with a higher risk when switching from anti-programmed death ligand-1 (PD-1)/PD-L1 to anti-CTLA-4.¹⁷ Given the paucity of prospective data, clinical decisions must be individualized based on the severity of the initial colitis episode, the oncologic necessity of continued ICI therapy, and the availability of alternative cancer treatments.

An important concern in managing ICI colitis is whether immunosuppressive therapy compromises the antitumor efficacy of checkpoint inhibitor therapy. For corticosteroids, preclinical and clinical data suggest that prolonged exposure to high-dose courses may dampen antitumor responses, and one retrospective analysis reported an association between higher initial corticosteroid doses and reduced survival when

controlling for age and cancer type.²¹ In contrast, preclinical mouse models have paradoxically shown that TNF- α blockade can improve antitumor responses to ICI therapy, possibly by reducing TNF-induced apoptosis of tumour-specific T cells.^{22,23} For vedolizumab, the gut-selective mechanism is theoretically expected to spare systemic antitumor immunity, though it may interfere with mucosal antitumor responses in GI malignancies.⁵ At present, adequately controlled human studies are lacking, and the effects of either agent on antitumor responses remain uncertain.^{5,22}

Practical Synthesis

Three questions provide a practical framework for managing ICI colitis: when to escalate therapy, which agent to select, and how long treatment should be continued (**Figure 1** outlines the escalation pathway). Escalation to SIT should be triggered by steroid-refractory disease (no improvement after ~72 hours of intravenous corticosteroids) or steroid-dependent disease (recurrence on taper). However, earlier escalation should be considered in patients with endoscopic ulceration or markedly elevated stool biomarkers. The choice between infliximab and vedolizumab should be guided by clinical context: infliximab for acute, severe presentations requiring rapid control; vedolizumab when gut-selective immunosuppression is preferred, particularly if ICI rechallenge is planned or systemic infection risk is a concern. A minimum three-dose induction course is recommended, with treatment duration guided by calprotectin normalization and/or endoscopic remission rather than by a fixed schedule.

For patients resuming ICI therapy, concurrent maintenance vedolizumab should be considered to reduce recurrence risk. Throughout all stages of management, the overarching goal is to minimize cumulative steroid exposure.

The ongoing randomized trial comparing infliximab and vedolizumab (NCT04407247) is expected to provide the first prospective comparative efficacy data in ICI colitis. However, the currently available preliminary results are limited to 19 patients, and longer follow-up is needed.¹³ Whether upfront biologic therapy in high-risk patients improves outcomes over the current sequential approach requires further evaluation; the real-world data remains hypothesis-generating but not definitive.

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Drug-induced Lupus Erythematosus: **When to Suspect and How to Diagnose**

Catherine Ivory, MD, PhD, FRCPC

Key Takeaways

1. Drug-induced lupus is rare but can occur after prolonged exposure to medications commonly used in gastroenterology, namely proton pump inhibitors and anti-TNF alpha biologic agents.
2. Autoantibodies (ANA and dsDNA) are commonly observed with the use of anti-TNF alpha biologic agents. However, drug-induced lupus should be suspected in the presence of symptoms, primarily rash or arthritis.
3. Clinical manifestations of drug-induced lupus are milder than those of systemic lupus erythematosus and should resolve with cessation of the offending medication.

Introduction

Drug-induced lupus erythematosus (DILE) represents a lupus-like clinical presentation associated with medication use that, by definition, resolves when the offending drug is discontinued.¹ DILE accounts for approximately 10% of "lupus" cases.² The first reported case of DILE was described by BJ Hoffman in 1945, involving

a lupus-like presentation following treatment with sulfadiazine.³ In the following years, similar presentations were reported of cutaneous rashes from anti-hypertensive and anti-arrhythmic agents, with both procainamide and hydralazine listed as high-risk medications for the development of DILE. Although these two medications are prescribed less frequently today, over 100 other medications have been listed in association with DILE, including

more recent therapies such as anti-tumour necrosis factor (TNF) alpha biologic agents and cancer immunotherapies.⁴

For clinicians, diagnosis can be difficult due to the lack of clear diagnostic criteria, patients exposed to polypharmacy with several potential offending drugs, and some patients with pre-existing autoimmune disease. This review summarizes the current understanding of the clinical presentations of DILE, discusses when the diagnosis should be considered, and examines the clinical and serologic differences between anti-TNF alpha-induced lupus and idiopathic systemic lupus erythematosus.

Classification and Clinical Presentation

There are no standard diagnostic criteria for DILE. In general, patients who develop new lupus-like symptoms should be evaluated for possible DILE.⁵ It is important to consider the following factors that support the diagnosis:

- Any prior history of lupus or DILE before drug initiation
- Substantial exposure to the medication, typically over months to years
- At least one objective clinical finding consistent with lupus (i.e. rash or arthritis)
- Appearance of new autoantibodies, such as anti-nuclear antibodies (ANA) and/or anti-double-stranded DNA (dsDNA)
- Symptoms should improve after discontinuation of the drug

DILE can be grouped into three clinical patterns:

- 1. Drug-induced-Systemic Lupus Erythematosus**—common with biologic agents, can present with fever, arthritis, serositis and rash.
- 2. Drug-induced Subacute Cutaneous Lupus Erythematosus**—most common presentation, with new-onset erythematous inflammatory rash, consistent with lupus on biopsy. Often associated with proton pump inhibitors and hydrochlorothiazide.
- 3. Drug-induced Chronic Cutaneous Lupus Erythematosus**—rare presentation seen in older adults, often associated with fluorouracil agents or non-steroidal anti-inflammatory drugs.

DILE should be suspected particularly if the individual has long-term exposure to a known possible culprit medication particularly with symptoms in the absence of an alternate diagnosis. An up-to-date list of all medications and their start date if possible is essential for identifying culprit agents. Although approximately 100 drugs have been implicated in DILE,⁴ the most commonly prescribed drug categories include: **1)** proton pump inhibitors, which are known to cause drug-induced skin rashes, **2)** anti-hypertensive agents, including beta-blockers, ace inhibitors, calcium channel blockers, thiazide diuretics, and hydralazine, which have been associated with lupus-like rashes and **3)** anti-TNF alpha biologic agents which can cause rash, arthritis, and, less commonly, systemic symptoms. Among the anti-TNF alpha biologic agents, infliximab, etanercept and adalimumab are most frequently associated with DILE.

Rashes are the most common clinical presentation of DILE. Subacute cutaneous lupus-like rashes often occur in a photo-distributed pattern, primarily on the face, neck, and extremities. These lesions may appear as a macular/papular or psoriasiform rash, which could be suitable for skin biopsy. However, skin biopsy findings cannot distinguish between drug-induced and idiopathic lupus⁶ except in cases with a clear presence of eosinophilic infiltrates. Rarely, DILE may present with lower-extremity purpura or erythema nodosum. In such cases, further investigation is warranted to rule out infection or vasculitis.

Arthritis is the next most common symptom of DILE, typically presenting with features including pain, swelling, and stiffness of the affected joints. While idiopathic lupus arthritis typically involves the small joints of the hands, DILE can involve small and large joints but typically is not associated with inflammatory back pain or discitis. Pain in general and myalgias are common with DILE and are reported in up to 90% of patients, which can account for symptoms of back discomfort and arthralgias without evidence of specific swelling.⁷ Generally internal organ involvement is extremely rare in DILE. Serositis has been reported in cases of anti-TNF-alpha induced lupus; however, its presence should prompt an extensive work up to exclude infectious causes, particularly underlying autoimmune diseases, such as inflammatory bowel disease or rheumatoid arthritis.⁸

	Systemic Lupus Erythematosus (idiopathic)	Drug-Induced Lupus Erythematosus	Anti-TNF alpha Induced Lupus
Male: Female	1:9	1–2:1	1:1
Age	18–45	>45	>45
Serology	ANA Anti-histone (20–30%) dsDNA (IgG) Anti-Smith Anti-SSA/RO (30–40%) Low C3/C4	ANA (anti-histone 75–95%) Anti-SSA/RO (5%) Normal C3/C4	ANA (anti-histone<50%) dsDNA (IgM) Low C3/C4 Anti-SSA/RO
Manifestations (common)	Malar rash Photosensitivity Alopecia Mucosal ulcers Arthritis Serositis Nephritis Cytopenia Fever/lymphadenopathy	Rash Arthralgia or arthritis Fever Myalgia	Rash Serositis Arthritis Fever

Table 1. Distinguishing Features of Systemic Lupus Erythematosus, Drug-Induced Lupus Erythematosus, and Anti-TNF-Alpha-Induced Lupus; *courtesy of Catherine Ivory, MD, PhD, FRCPC.*

Abbreviations: ANA: anti-nuclear antibodies; dsDNA: anti-double-stranded DNA antibodies; IgG: immunoglobulin G; SSA: Sjögren's Syndrome-related Antigen A

Comparison of Systemic Lupus Erythematosus, Drug-Induced Lupus Erythematosus and Anti-TNF-alpha-Induced Lupus

Although idiopathic systemic lupus erythematosus (SLE), DILE, and anti-TNF-alpha-induced lupus (ATIL) share many clinical features, several distinctive patterns can help distinguish these entities (**Table 1**).

Clinical presentation

Overall, idiopathic SLE has a female predominance and is most commonly diagnosed during the reproductive years, whereas DILE typically presents later in life. DILE has been reported to have a slight male predominance, likely due to increased cardiovascular comorbidities requiring treatment with medications known to trigger the condition.⁹ ATIL also tends to be diagnosed at an older age than idiopathic SLE, although it may be observed across a broader age range due to the expanding use of these biologic therapies.

DILE most commonly presents with a rash, and at times arthritis and fever. Unlike SLE, there are fewer reports of malar rash, mucosal ulcers, or alopecia. Among patients with ATIL, 80% present with rashes,⁷ and arthritis is reported more frequently than in DILE. Although rare, cases of serositis have also been described in ATIL. Lupus nephritis, central nervous system involvement, and cytopenias are exceedingly rare in DILE,¹⁰ whereas these features are well-recognized in idiopathic SLE. Notably, renal involvement develops in up to 50% of patients with idiopathic SLE.¹¹

Serological evaluation

It is important to recognize that the absence of ANA, anti-histone antibodies, or anti-dsDNA does not exclude the possibility of DILE. Nevertheless, ANA positivity is reported in 90–100% of cases,¹² leading some authors to propose its inclusion as part of the diagnostic criteria. However, the presence of autoantibodies alone does not indicate pathology; therefore, a clear history and clinical examination is necessary to interpret laboratory findings. In idiopathic SLE, patients typically demonstrate several high

titre, high affinity autoantibodies, including ANA and anti-dsDNA antibodies. In contrast, DILE is most characterized by ANA positivity, frequently accompanied by anti-histone antibodies, whereas anti-dsDNA antibodies are uncommon. It should be noted, however, that anti-histone antibodies can also be detected in 20–30% of idiopathic SLE patients.¹³ Anti-dsDNA antibodies are commonly detected in ATIL; however, studies have shown that these antibodies are of the immunoglobulin (Ig)M subtype, exhibit lower affinity, and are not thought to be pathogenic compared to the high affinity IgG anti-dsDNA antibodies reported in SLE.¹⁴ Anti-Sjögren's Syndrome A (SSA/RO) antibodies can be detected across SLE, DILE, and ATIL, although at much lower titres than those observed in SLE. Their presence in each condition has been associated with the development of rashes.¹⁵ Hypocomplementemia is unique to SLE. Although reduced complement levels have been reported in some patients with ATIL, they are not observed with DILE.

Autoantibodies often persist even after the offending drug has been discontinued and clinical symptoms have resolved. As a result, repeat testing is not indicated unless new symptoms emerge. Lower-titre antibodies may decline, become negative, or fluctuate over time, particularly in patients receiving immunosuppressive treatments. Importantly, patients can be reassured that a diagnosis of DILE or ATIL does not result in an increased risk of developing SLE.⁵

Diagnostic Approach

A systematic evaluation of the temporal relationship between drug initiation and symptom onset, the types of symptoms, and the exclusion of alternative diagnoses is key for confirming DILE (Figure 1).

- **Assess Clinical Manifestations:** Evaluate for the presence of arthritis (with ultrasound assessment for synovitis when swelling is not clinically apparent), rash (consider skin biopsy), and other manifestations requiring investigations, such as chest X-ray for pleuritic symptoms, or electrocardiography and echography for suspected pericarditis. Concurrently, alternative diagnoses, including infection and cancer, should be excluded.
- **Evaluate the Timing and Type of Drug Exposure:**
 - Acute symptom onset (7–14 days post new medication) → suggestive of a drug reaction rather than DILE
 - Chronic symptom onset (months to years after drug initiation) → supports consideration of DILE
 - Drug is known to potentially cause DILE
- **Review Serology Findings:**
 - ANA positive and anti-dsDNA positive → may suggest ATIL.
 - ANA positive and anti-histone antibody positive → supports a diagnosis of DILE
- **Discontinue Offending Drug:**
 - **Treat symptoms of DILE or ATIL:** NSAIDs for arthritis, topical steroids for rashes, and corticosteroids for more severe presentations (serositis)
- **Assess for Resolution:**
 - DILE → symptoms typically resolve within weeks
 - ATIL → symptoms typically resolve within 2–3 months, although recovery time can vary depending on the patient and the type of causative medication
- **Consider Alternate Therapy:** if ongoing treatment remains indicated

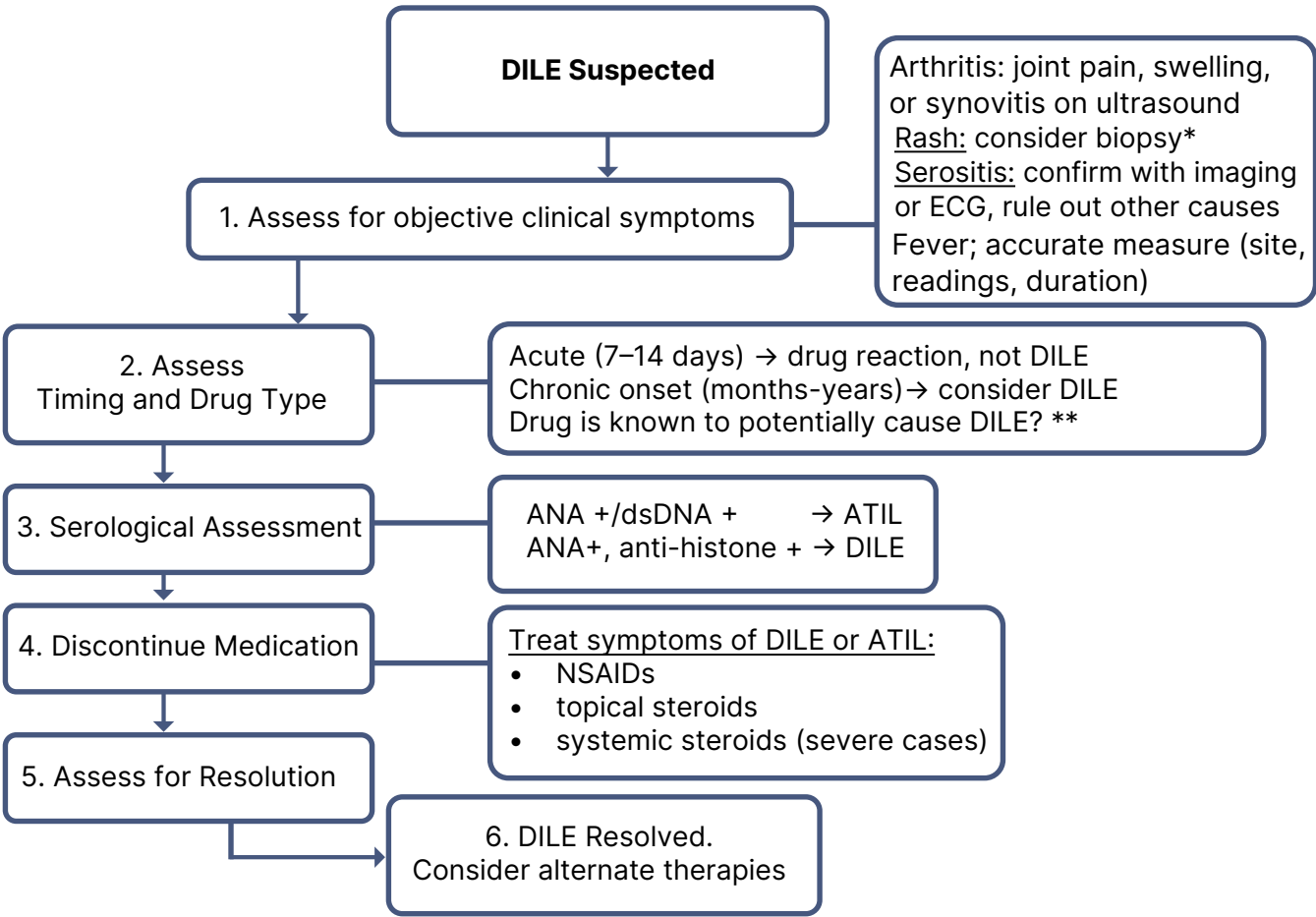


Figure 1. Approach to Drug-Induced Lupus Erythematosus (DILE); courtesy of Catherine Ivory, MD, PhD, FRCPC.

* Skin biopsy of affected lesions should provide histological findings consistent with lupus.
** For a list of drugs known to be associated with DILE.^{4,5}

Abbreviations: ECG: electrocardiogram; ANA: anti-nuclear antibodies; ATIL: anti-tumour necrosis factor- induced lupus; DILE: drug-induced lupus erythematosus; dsDNA: anti-double-stranded DNA antibodies; ATIL: Anti-TNF-induced lupus; NSAIDs: non-steroidal anti-inflammatory drugs.

Other Considerations for ATIL

- Patients with inflammatory bowel disease, rheumatoid arthritis, or spondyloarthropathies may have baseline ANA positivity. ANA positivity was found at baseline in 43.6% of rheumatoid arthritis patients and increased to 73% after infliximab exposure, whereas anti-dsDNA antibodies were only present in 9.5% of patients after treatment.¹⁶ After 6 months of infliximab therapy for various approved indications including inflammatory bowel diseases, ANA was positive in 69.4% of patients but only one patient (1/268) developed ATIL.¹⁷ For this reason, some experts have suggested obtaining baseline reference ANA and anti-dsDNA testing prior to starting anti-TNF alpha therapy.^{18,19}
 - A positive baseline result does not preclude the use of biologic therapy.
 - Developing positive ANA or anti-dsDNA antibodies after initiating anti-TNF therapy is common and, in the absence of clinical symptoms to suggest ATIL, does not predict the development of ATIL or warrant discontinuation of the medication.
 - No further monitoring or testing for ANA or dsDNA is required unless DILE or ATIL is suspected.
- If ATIL is confirmed, switching to a biologic with an alternative mechanism of action is recommended. However, in selected patients for whom anti-TNF alpha therapy remains the best therapeutic option, continued use may be considered in individuals who experience only mild ATIL symptoms, such as limited rash or mild arthritis.
 - Rechallenge with the same medication is discouraged, as it could lead to recurrence of DILE within days to weeks and should only be undertaken with close clinical monitoring.
- Infliximab has been associated with a higher risk of auto-antibody production, likely based on its chimeric antibody structure. Nevertheless, the reported rate of ATIL remains low, occurring in 0.5–1% of users, indicating that it is a rare phenomenon and that anti-TNF alpha therapy remains a safe therapeutic option.¹⁸

Conclusion

DILE remains a clinical diagnosis, as no clear diagnostic criteria exist. However, it should be strongly suspected in patients who develop new-onset rash or arthritis following prolonged drug exposure. ANA positivity, often corresponding to the presence of anti-histone antibodies, is common in DILE, whereas anti-dsDNA antibodies are more frequently observed in ATIL. Exclusion of alternate causes for the symptoms is essential when DILE is suspected. When DILE is correctly identified, symptoms will resolve following discontinuation of the offending medication. Therefore, early identification of DILE is critical to facilitate prompt drug discontinuation and often requires a multidisciplinary approach involving gastroenterology, dermatology, and rheumatology.

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Management of Mild Crohn's Disease in 2026

Nancy Fu, MD, MHSc, FRCPC

Key Takeaways:

Mild Crohn's disease patients have limited anatomical disease involvement with no severe endoscopic lesions, and absence of stricturing, fistulizing or perianal features. They are usually older, ambulatory, eating well and have no prior surgery, abnormal biochemistry or signs of systemic toxicity.

Non-pharmacological management for mild Crohn's disease can include dietary interventions, NSAID and tobacco avoidance. Pharmacotherapy may include budesonide, sulfasalazine and immunomodulators. Mesalamines should not be used.

Mild Crohn's disease can be managed with close monitoring only. It should include regular clinical and biochemical evaluations with endoscopy, cross sectional studies and health maintenance assessments at recommended intervals.

Introduction

Crohn's disease (CD) is an idiopathic inflammatory condition that in most cases follows a progressive disease course. However, approximately 20% of patients with CD have

mild disease and are at low risk of progression.¹ In a retrospective cohort study among 473 patients with mild CD on presentation, up to 56% maintained a mild phenotype after 5 years of follow-up.² When managing mild CD, it is important to focus on accurate diagnosis, shared therapeutic goals, close monitoring, and health maintenance (Figure 1).

Diagnosis

Mild CD is characterized by limited anatomical disease involvement with no severe endoscopic lesions (Simple Endoscopic Score for Crohn's Disease [SES-CD] 3 to 6; Crohn's Disease Endoscopic Index of Severity [CDEIS] score of 3 to 9), and absence of stricturing, fistulizing or perianal features. Patients with mild CD are usually older (>30 years), ambulatory, able to tolerate oral intake, and have no prior surgery or systemic signs of toxicity such as fever, weight loss, or dehydration. Their biomarkers are generally normal or slightly elevated.³ In addition to endoscopy, small bowel and perianal imaging studies should be performed to ensure accurate

Management of Mild Crohn's disease in 2026



Figure 1. Management of mild Crohn's disease in 2026; created using ChatGPT (OpenAI, GPT-4o, Feb 2026 version) to generate a conceptual layout; finalized and verified by the author (Nancy Fu, MD, MHSc, FRCPC).

diagnosis. A comprehensive assessment is crucial for risk stratification, as some patients with otherwise mild CD may still be at increased risk of complications in the presence of younger age at diagnosis, ongoing tobacco use, early steroid dependence, upper gastrointestinal tract or small bowel involvement, or carry high-risk genetic and serological features.⁴

Goals and Therapies

The treat-to-target framework for management of CD, as described in STRIDE-II,⁵ is equally applicable for patients with mild CD. Providers can consider using a shared decision making process with patients to elicit preferred therapeutic approaches.⁶ Although the treatment armamentarium for CD has expanded, many advanced therapies are not justifiable for this low-risk population, considering their cost and potential adverse effects.

Controlled ileal-release budesonide delivers targeted therapy to the ileum and right colon with low systemic corticosteroid effects, making it a useful, localized induction agent for mild CD.^{7,8} It is significantly more effective than placebo at inducing remission after 8 weeks (47% vs. 22%; risk ratio [RR] 1.93, 95% confidence interval [CI] 1.37 to 2.73), although it is less effective than conventional steroids (52% vs. 61%; RR 0.85, 95% CI 0.75 to 0.97). A typical budesonide induction dose consists of 9 mg orally once daily for 2 months, followed by 6 mg daily for one month, then 3 mg daily for one month. A second steroid course can be considered in patients who relapse upon steroid withdrawal. However, failure to respond to treatment suggests a higher risk of disease progression and should prompt consideration of advanced therapies.

Sulfasalazine (3 to 6 g daily orally in divided doses) is useful for treating symptomatic colonic CD. In a systematic review, sulfasalazine demonstrated a non-significant trend toward greater remission rates over placebo (45% vs. 29%; RR 1.38, 95% CI 1.00 to 1.89).⁹ However, a network meta-analysis reported that sulfasalazine was not significantly superior to any therapy including placebo.¹⁰ Despite limiting supporting evidence, 5-aminosalicylates (5-ASAs) continue to be widely prescribed for management of CD. Comprehensive reviews have failed to show efficacy of 5-ASAs compared to placebo in

inducing remission, achieving mucosal healing, or maintaining remission.⁹⁻¹¹ Immunomodulators, azathioprine (AZA), 6-mercaptopurine (6-MP) and methotrexate (MTX) can be used as maintenance therapy for those with active disease after an initial response to steroid induction. AZA was superior to placebo for maintenance of remission over a 6-to-18-month period (73% vs. 62%; RR 1.19, 95% CI 1.05 to 1.34), although no significant differences were observed between AZA or 6-MP and 5-ASA or sulfasalazine. However, use of AZA/6-MP is less common as maintenance therapy because of their association with an increased risk of adverse events.¹² Intramuscular MTX was superior to placebo (65% vs. 39%; RR 1.67, 95% CI 1.05 to 2.67), whereas low-dose oral MTX showed no significant difference compared to placebo or 6-MP.¹³ Typical doses are AZA 2 to 2.5 mg/kg/day orally, 6-MP 1 mg/kg/day orally, and MTX up to 25 mg weekly by subcutaneous or intramuscular injection, or 15 to 25 mg/week orally. Given the need to balance effectiveness and adverse effects, some clinicians may instead consider biologic agents with more favourable safety profiles for maintenance therapy.

Some patients with mild CD may opt to forgo maintenance medical therapy. This approach is most suitable for motivated patients that engage in proactive disease monitoring. Treatments used for symptomatic relief often include anti-diarrheal agents and dietary modifications. Several dietary therapies have recently been explored for the management of CD.¹⁴ The Mediterranean diet remains the base of dietary recommendations, focusing on fresh fruits and vegetables, monounsaturated fats, complex carbohydrates, and lean proteins. Adherence to a Mediterranean diet for at least 6 months has been associated with improvements in biomarkers and quality of life among patients with CD.¹⁵ Exclusive enteral nutrition is well-established in the pediatric population as a steroid sparing induction method. The Crohn's disease exclusion diet may be an effective therapy for induction of clinical remission and endoscopic response in mild to moderate CD of relatively short duration.¹⁶

Disease Monitoring

Many patients with mild, asymptomatic CD can be managed with monitoring alone. However, providers should be mindful that

CD symptoms may not correlate with disease activity and asymptomatic patients remain at risk of silent disease progression.¹⁷ In a cohort of 60 patients with incidentally diagnosed asymptomatic CD, 88.3% did not receive any treatment after diagnosis, 9.4% experienced a disease flare, 7.5% had developed a change in disease phenotype, and 6% required surgery in subsequent follow-up (median 4.5 years).¹⁸

Patients with CD should undergo regular monitoring with clinical assessments and biochemical marker testing every 6 to 12 months after induction and during remission. Common clinical assessment tools include the Harvey-Bradshaw Index (HBI) and the Crohn's Disease Patient-Reported Outcome 2-item measure (CD-PRO2), which is a two-item subscore derived from the Crohn's Disease Activity Index (CDAI).¹⁹ Recommended laboratory tests include a complete blood count, metabolic and liver panels, albumin, ferritin, renal function, C-reactive protein, and fecal calprotectin. Periodic assessment of micronutrients (vitamins A, D, E, K, B12, and folate, as well as iron, zinc, and magnesium) can be considered depending on disease location. Ileocolonoscopy should be performed within 12 months after diagnosis to ensure mucosal healing, and subsequently as prompted by assessment of active disease and planned according to the dysplasia surveillance schedule. Cross-sectional imaging studies can also be considered every 1 to 3 years.²⁰ Intestinal ultrasound is emerging as a highly accurate, noninvasive bedside tool for the evaluation of CD activity²¹ and is increasingly being used as an alternative to endoscopy and imaging studies for assessing active disease.

Health Maintenance

A proactive health maintenance approach is an important component of care in this low-risk group. Regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been found to increase the risk of CD exacerbation,²² while smoking has been associated with greater CD progression and higher rates of complications.²³ Accordingly, limiting NSAID use and promoting smoking cessation should be disease-modifiable care strategies. Other important aspects of preventive care include vaccinations, cancer screening, and assessment of mental health and nutritional status.²⁴

Patients with mild CD represent a unique group that can benefit from behaviour modifications, dietary interventions, and selected use of pharmacological therapies. Ongoing monitoring remains essential to detect disease progression and guide appropriate treatment optimization.

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Incidental Finding of Terminal Ileum Inflammation on Screening Colonoscopy: Approach to Diagnosis and Workup

Karen I. Kroeker, MSc, MD, FRCPC

Key Takeaways
Incidental terminal ileitis is identified in ~1.6% of screening colonoscopies.
Isolated terminal ileal inflammation without symptoms often resolves without treatment.
The presence of symptoms, not chronicity on biopsies, is the best predictor of isolated ileitis progressing to overt Crohn's disease.
Use a fecal calprotectin cutoff of >200 µg/g to identify inflammation in isolated ileal Crohn's disease.

Introduction

The incidental finding of terminal ileal inflammation on screening or non-diagnostic colonoscopy poses a diagnostic and management dilemma for all gastrointestinal endoscopists. The question of whether this finding represents inflammatory bowel disease (IBD), namely Crohn's disease, is often postulated. This paper outlines a pragmatic approach to the evaluation and management of an incidentally identified finding of terminal ileitis on screening colonoscopy.

Review of the Literature

In Canada, colorectal cancer (CRC) screening is offered to asymptomatic average risk individuals aged 45/50–75 years (In 2026, the age to start screening in Canada varies by province with some offering screening at age 45 and others at age 50). Screening is primarily based on fecal immunochemical testing (FIT), with colonoscopy reserved for FIT positive individuals or those at increased risk of CRC.¹ Other jurisdictions have adopted age 45 as the start for average risk screening. However, patients undergoing screening colonoscopy are not always truly asymptomatic and may report symptoms of rectal bleeding, diarrhea, or abdominal pain. As these symptoms can be intermittent or gradual in onset, patients often downplay or ignore them. The differential diagnosis of a positive FIT result is broad, and includes any condition that leads to bleeding in the digestive tract, such as colon cancer, polyps, hemorrhoids, diverticulosis, and angiodysplasia. As both FIT and fecal calprotectin (FCP) can be used to identify mucosal healing in Crohn's disease,² individuals with a positive FIT result may also have bowel inflammation accompanied by an elevated FCP level.

The differential diagnosis of ileal inflammation and ulceration is broad and includes infection, drug-induced (e.g. nonsteroidal anti-inflammatory drug-related), intestinal tuberculosis (TB), Behçet's disease and malignancy, in addition to Crohn's disease.^{3,4} The presence or absence of symptoms—including abdominal pain, weight loss, diarrhea, bleeding, and oral or genital ulceration—are important in helping to determine if the findings represent Crohn's disease.

A systematic review reported a pooled prevalence of 1.6% (range, 0.04–6.77) for incidentally detected terminal ileitis on non-diagnostic colonoscopy among asymptomatic patients undergoing colon cancer screening, with terminal ileitis defined as 'macroscopic erythema, erosion, ulceration, or non-specific inflammation.'⁵ Long-term follow-up of one-quarter of these patients showed that progression to overt Crohn's disease was rare, although a small proportion subsequently developed symptoms. In a large (>40,000 patients) single-centre study of a CRC screening cohort that included FIT positive individuals or those undergoing surveillance colonoscopy for prior polyps, incidental IBD was found in 0.15% of procedures. Of these cases of incidental IBD, two-thirds (40/60) were Crohn's disease, and 39/40 had isolated ileal involvement.⁶ During a mean follow-up of ~2 years, only 3 Crohn's patients developed symptoms and were started on therapy after symptom onset. Notably, isolated terminal ileal ulcerations in asymptomatic individuals often improve or resolve without-treatment.^{7,8}

In a South Korean study of patients with symptomatic localized terminal ileitis at a referral hospital, a specific diagnosis was established in two-thirds of cases. Crohn's disease was the most common diagnosis (42%), followed by Behçet's disease (28%) and infection (14%), with drug-induced causes, TB, and other diagnoses accounting for the remainder.¹¹ Abdominal pain was present in most patients with Crohn's, disease, Behçet's disease, and non-TB infection, while diarrhea occurred in approximately half of those with Crohn's disease or infection. Oral ulceration was identified in most patients with Behçet's, disease, in one-sixth of those with Crohn's disease, and in 30% of those with infection. In contrast, genital ulcers were exclusively observed in those with Behçet's disease.¹¹

Role of Biopsy (Pathology), Fecal Calprotectin and Intestinal Ultrasound

The finding of ileal inflammation at endoscopy often prompts biopsy to assess the degree of inflammation and to identify histologic signs of chronicity. However, a biopsy study of individuals with endoscopic and histologic ileal abnormalities reported that the presence of symptoms was the best predictor of progression to Crohn's

disease (p<0.001). In contrast, asymptomatic individuals with ileitis, even with chronicity findings on histology, rarely progressed to overt Crohn's disease.⁹

FCP is commonly used to determine mucosal healing in those with a known diagnosis of Crohn's disease. However, it is important to note that for those with isolated ileal disease, an FCP cutoff of 200 µg/g may be more appropriate than the conventional cutoff of 250 µg/g.¹² Repeated assessment of symptoms and FCP testing at one year and thereafter as clinically indicated, can aid in ongoing monitoring for the development of Crohn's disease over time.

In a retrospective study of a subset of patients with non-specific ileitis identified at endoscopy who underwent intestinal ultrasound, no patient with a normal bowel wall thickness (<3 mm) was subsequently diagnosed with Crohn's disease.¹⁰ Of the patients who met the criteria for nonspecific ileitis, 66 were followed up with another modality [median follow-up time of 370 days (IQR 173–911)]. Thirty-five patients were followed up with intestinal ultrasound (≤6 months from colonoscopy), and 31 had colonoscopy (52%, n=16), a gastrointestinal ultrasound that was taken ≥ 6 months after the colonoscopy (29%, n=9), or other cross-sectional radiology (19%, n=6) [CT enterography (CTE) in 1 and magnetic resonance enterography (MRE) in 5]. Although the cohort included patients with iron deficiency anemia, only 5.4% ultimately developed Crohn's disease, with most diagnosed in the first year of follow-up at a median of 148 (range 27–603) days after colonoscopy. These findings raise the possibility of using intestinal ultrasound as an adjunct tool to exclude Crohn's disease in patients with incidental ileitis.

Management

It is important to remember that even when mild ileal Crohn's disease is diagnosed, current evidence does not support the use of biologics or small molecule therapies as first-line treatment. Because advanced therapies for Crohn's disease are approved for moderate-to-severe disease, the optimal approach to management of mild Crohn's disease, especially isolated ileal Crohn's disease, remains less clearly defined. Mild ileal Crohn's

disease is characterized by normal laboratory parameters, aside from mildly elevated biomarkers (FCP, c-reactive protein), a Simple Endoscopic Score for Crohn's disease score of 3–6, and the absence of significant systemic signs or weight loss.¹³ Budesonide 9 mg daily for 4–8 weeks is an appropriate treatment, followed by re-assessment at 3 months. Patients who respond can often be managed with supportive care (diet, antidiarrheals) and ongoing monitoring at one year.¹³⁻¹⁵ Symptomatic patients with ongoing inflammation may require additional therapy with prednisone, immunosuppressants, and/or advanced therapies. Re-assessment at one year or if symptoms develop is prudent.

Approach and Workup of Incidentally Found Terminal Ileitis

Figure 1 depicts an approach and monitoring strategy for diagnostic workup and management of patients with incidentally identified terminal ileitis.

Summary and Conclusions

The finding of terminal ileitis identified on screening colonoscopy has a broad differential diagnosis and should prompt a re-assessment for symptoms, including evaluation for extraintestinal manifestations of IBD and Behçet's disease. Available evidence suggests that only a minority of patients with incidentally identified mild ileitis on colonoscopy (~5%) will develop Crohn's disease. Initial evaluation should include laboratory assessment with a complete blood count, c-reactive protein, and FCP should also be completed. Because isolated ileal disease is often associated with lower FCP levels, a threshold of >200 µg/g might be more appropriate than conventional cutoffs. Asymptomatic patients rarely develop overt Crohn's disease, even if biopsies show signs of chronicity. Intestinal ultrasound assessment may further aid in risk stratification, with a bowel wall thickness <3 mm suggesting a low likelihood of Crohn's disease. The presence of symptoms is the most important predictor of patients with incidentally diagnosed terminal ileitis progressing to overt Crohn's disease.

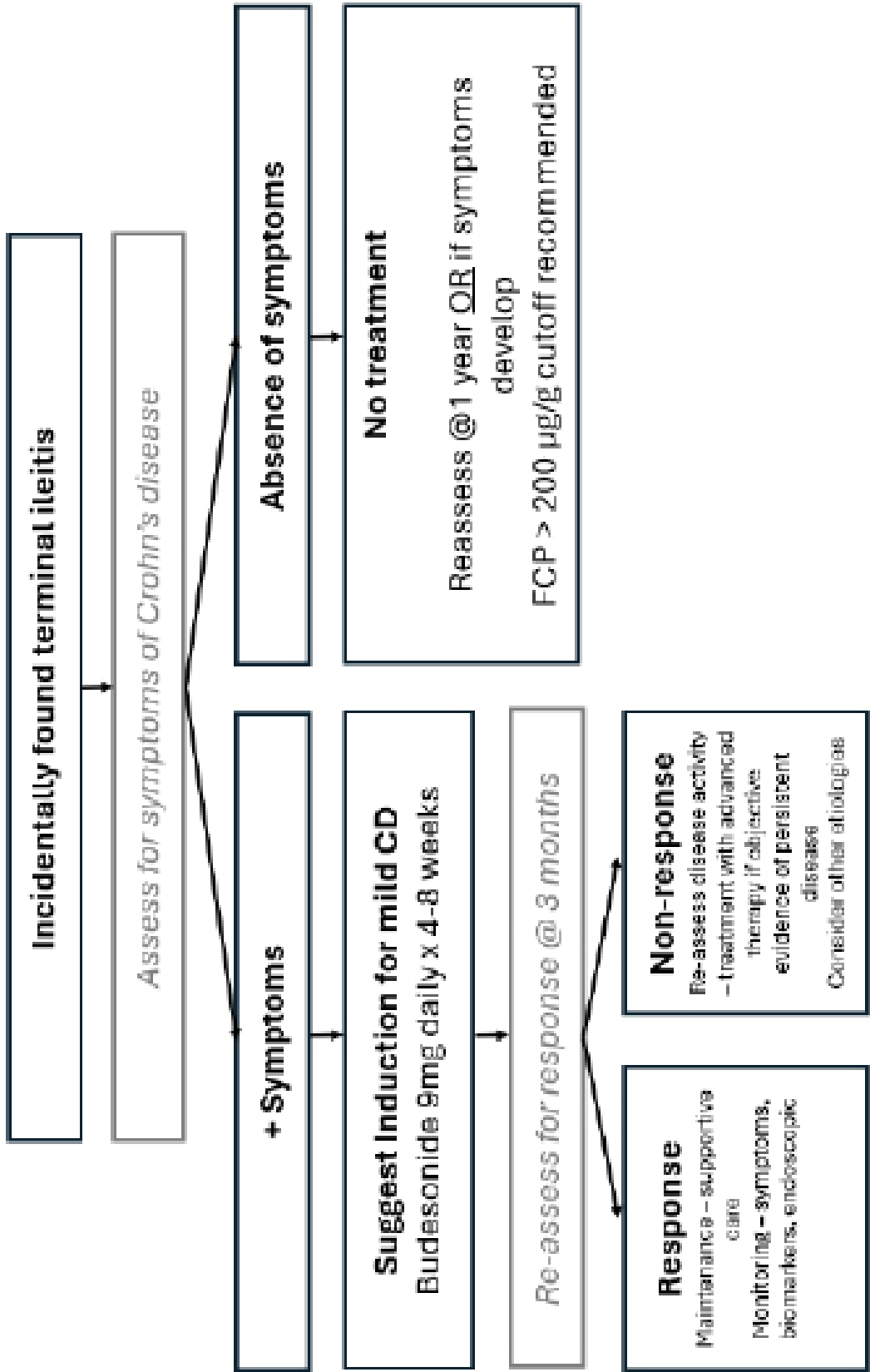


Figure 1. Pragmatic approach to incidentally identified findings of terminal ileitis; courtesy of Karen I. Kroeker, MSc, MD, FRCPC.
Abbreviations: CD: Crohn's disease; FCP: fecal calprotectin

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